

Applicability limitations and mismatched populations of chimeric antigen receptor T cell immunotherapy

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Abstract. In the past ten years, the research have witnessed the emergence of new tumor immune precision targeted therapy CAR-T cells, which has opened up a new path for tumor treatment. CAR-T cell therapy has been approved for the treatment of hematological tumors, but its role in solid tumors is still unsatisfactory, so many studies have explored combination therapies to improve the efficacy of CAR-T therapy in solid tumors, and although CAR-T cell therapy has a good effect on the treatment of hematologic tumors, there are still non-expressed cases.³ Combination immunomodulators. Chimeric antigen receptor T cell therapy is a new type of immunotherapy in the field of tumors, and CAR-T therapy for solid tumors faces many challenges due to the immunosuppressive microenvironment of solid tumors and the heterogeneity of antigen expression. This paper mainly focuses on the range of treated people of chimeric receptor T cells, and roughly summarizes some of the suitable populations through a large number of literature readings and fusion citations, which aims to help more accurately locate the treated population.

Keywords: T-Cells, treatment, therapy, antigen, tumors.

1. Introduction

Chimeric antigen receptor T cells (CAR-T) is a new cell immunotherapy technology that has developed rapidly in recent years. However, there has been no accurate judgment about the people treated with this treatment, so there is no accurate acceptance status statement when receiving this treatment. This article summarizes part of the acceptance qualification in general terms by consulting some materials to achieve a partial induction.

Chimeric antigen receptor (CAR) is a molecular modifier that enables T cells modified with it to have an antibody sequence that recognizes tumor antigens and has specific recognition and killing activity against tumors. From the 1990s to the present, the research on chimeric antigen receptor T cell (CAR-T) immunotherapy has gone through nearly 30 years, including the proposal of concepts, design, basic research, animal experiments, clinical trials, etc. From the first generation of CAR-T to the current third and fourth generation of CAR-T, the types of CAR-T have been continuously increasing, demonstrating greater advantages in treating various malignant diseases of the blood system. At present, CAR-T immunotherapy has significant efficacy in the treatment of hematological malignancies such as acute B-ALL, non-Hodgkin's lymphoma (NHL), and multiple myeloma (MM), and is considered one of the more advanced gene therapies[1].

In recent years, tumor immune cell therapy has no drug resistance, less toxic side effects, and remarkable curative effects. The past decade has witnessed the new tumor immunity precision targeted therapy CAR-T cells, opening up a new path for tumor treatment. CAR-T cell therapy has been approved for the treatment of hematological tumors, but its role in solid tumors is still unsatisfactory, so many studies have explored combination therapies to improve the efficacy of CAR-T therapy in solid tumors. Therefore, this article will first introduce the results of the synergistic effect of tumor immune cell therapy with combined immunomodulators in the clinical aspect, and the research progress in the treatment of solid tumors and hematological tumors[2].

2. Therapy and tumors

2.1. Overview

CAR-T therapy is chimeric antigen receptor T cell immunotherapy, English full name Chimeric Antigen Receptor T-Cell Immunotherapy. This is a new type of precision targeted therapy for the treatment of tumors, which has achieved good results in clinical tumor treatment through optimization and improvement in recent years, and is a very promising new tumor immunotherapy method that can be precise, rapid and efficient, and may cure cancer. T cells, also called T lymphocytes, are a kind of human white blood cells, derived from bone marrow hematopoietic stem cells, mature in the thymus, and then migrate to the human blood, lymph and surrounding tissues and organs to play immune functions. Its role is equivalent to that of a "warrior" in the human body, able to resist and destroy "enemies" such as infections, tumors, foreign bodies, etc. In the laboratory, technicians through genetic engineering technology, T cells activated, and equipped with positioning navigation device CAR (tumor chimeric antigen receptor), T cells, ordinary "warriors" into "super soldiers", that is, CAR-T cells, he uses its "positioning navigation device" CAR, specifically identify tumor cells in the body, and release a large number of a variety of effector factors through immunity, they can efficiently kill tumor cells, so as to achieve the purpose of treating malignant tumors. CAR T-cell therapy is effective in eradicating relapsed or refractory disease in some patients; However, treatment failure remains an obstacle. Although the loss of CD19 antigen in recurrent tumors is a drug-resistant mechanism, it is not the only way for tumors to escape. There are other mechanisms at play, such as disruption of de novo T cells for making autologous CAR-T, or disruption of them through the chronic inflammatory tumor environment after adoptive metastasis for expression[3].

2.2. Hematological tumors

First of all, from the perspective of hematological tumors, T cells extracted from cancer patients express CAR structure through gene editing, which can specifically target tumor surface antigens and can specifically kill tumors without relying on MHC. Lymphocytic leukemia is currently one of the most mature areas of CAR-T therapy, and a considerable number of clinical trial reports show that CAR-T targeting CD19 can significantly alleviate or even cure refractory and relapsible B lymphocyte malignancies, with a complete response rate of more than 83%. Some CAR-T treatments targeting CD19+ multiple myeloma stem cells have also achieved good results, and the patient's condition has been relieved after CAR-T infusion, and the remission lasts for 12 months. Although CD19 target is currently the antigen most used for lymphoid leukemia, the expression of CD19 on tumor cells is down-regulated and the gene mutation is down-regulated during treatment, resulting in a decrease in the therapeutic effect of CD19CAR-T. In a clinical trial, 40%~60% of lymphoma leukemia patients relapsed due to poor CAR-T persistence and CD19 clone loss. In another patient with relapse, 66%~100% did not express CD19. Therefore, although CAR-T cell therapy has a good effect on the treatment of hematological tumors, there are still cases of non-expression[4].

2.3. Solid tumors

The clinical research progress on solid tumors is different from hematological tumors, and the targets used to treat solid tumors are tumor-associated anti-gens (TAA) rather than tumor-specific antigens (TSA). Tumor-associated antigens are also expressed in normal tissues, so there is a potential risk of off-targeting, which is also a major problem in the application of targeted therapy for solid tumors in CAR-T therapy. There are differences in expression between solid tumor tissues and healthy tissues on these targets, and gene-edited CAR-T cells can have preferential killing properties for these cells with high expression of a certain antigen. Therefore, the selection of targets usually requires an overexpressed and relatively non-specific surface antigen, such as epidermal growth factor receptor variant III (EGFRv III). Therefore, CAR-T technology first relies on the careful selection of targets in dealing with solid tumors and also lies in the careful selection of experimental subjects[4].

2.4. Combined immunomodulators

Chimeric antigen receptor (CAR) T cell therapy is a new immunotherapy in the field of tumors, and CAR-T treatment of solid tumors faces many challenges due to the heterogeneity of the immunosuppressive microenvironment and antigen expression of solid tumors. There is growing evidence that CAR-T cell combination therapy can significantly improve prognosis and has good prospects. However, the true characteristics and mechanism of CAR-T cells combined with immunomodulators are not clear, so it is important to find its applicable population and use conditions[1].

3. Treatment

3.1. Suitable for the treatment of leukemia

Take an example of an experiment. About D19 chimeric antigen receptor (CD19 CAR) redirected adoptive T-cell immunotherapy for the treatment of relapsed or refractory B-cell non-Hodgkin lymphoma applications. Experimental data have proved that this therapy has a significant effect on the treatment of leukemia and can avoid the drawbacks of drug resistance. Recovery rates for B-cell non-Hodgkin lymphoma (NHL) are as high as 70%, and the current standard of care includes rituximab (chimeric anti-CD20 monoclonal antibody) in combination with chemotherapy (R-CHOP). However, patients who do not respond to first-line therapy or who develop resistance have a very poor prognosis. This means that optimal treatments need to be developed for relapsed/refractory B-NHL. Novel CD19-chimeric antigen receptor (CAR) T cell redirected immunotherapy is an attractive option for this subgroup of patients. Anti-CD19 CAR T-cell therapy is effective in a variety of leukemias and has yielded encouraging results in Phase I clinical trials in relapsed/refractory NHL. In more clinical trials, complementary therapies that may circumvent potential resistance mechanisms should be used with anti-CD19 T cells to prevent the recurrence of resistant strains[5].

3.2. Systemic B-cell lymphoma (SCNSL) with secondary central nervous system involvement may be appropriate

Systemic B-cell lymphoma (SCNSL) with secondary central nervous system involvement is difficult to treat and has a poor prognosis. Chimeric antigen receptor (CAR) T cells emerged as a powerful treatment for systemic lymphoma. To evaluate whether CAR T cells also represent a safe and effective treatment for SCNSL. The research retrospectively searched our institutional databases of patients with CD19-directed CAR T cell therapy with SCNSL. A total of 10 cases were identified, of which 7 patients had intracranial lesions and 3 patients had leptomeningeal disease. CNS staging 1 month after CAR T cell infusion showed disease response (stable disease, partial response, complete response) in 7 patients, of which 2 patients had a long-term complete response (20%). One patient had pseudoprogression that resolved under steroids. Reactions in diseases of the central nervous system were associated with reactions at 1 month. The median follow-up was 6 months, and the median overall and systemic progression-free survival was 7 months and 3 months, respectively. Six patients developed neurotoxic symptoms and three developed severe neurotoxicity ($\geq$ ASTCT grade 3). CAR T cells induce considerable antitumor effects in SCNSL, and the CNS response mirrors the systemic response. The appearance of neurotoxicity is similar to previous reports of patients with lymphoma without CNS involvement. Therefore, CAR T cells may represent an effective and safe treatment for SCNSL[6].

3.3. The treatment of primary liver cancer is very useful

Primary liver cancer has the characteristics of insidious onset and difficulty in early diagnosis, and the treatment methods are limited and the effect is not good. Chimeric antigen receptor (CAR) T cell therapy is gene-edited modified T lymphocytes to recognize tumor-specific antigens and activate T lymphocytes to exert tumor-killing effects. CAR-T cell therapy has made significant progress in the

treatment of hematological tumors and has also had good clinical efficacy in the field of solid tumors in recent years, although CAR-T cell therapy technology has developed from the first generation to the fifth generation, there are still many challenges in the field of solid tumors. This article will make a comprehensive review of the mechanism of CAR-T cell therapy for primary liver cancer and related research progress, including the current main targets of CAR-T cell therapy in the treatment of primary liver cancer GPC3, AFP, MUC1, NKG2D, CAR-T cell therapy and oncolytic virus, the emerging immune checkpoint inhibitors and other combination therapy, as well as the review of biological, preclinical and clinical studies of the above targets and treatment methods. The challenges and solutions of CAR-T cell therapy for primary liver cancer were summarized. It provides a reference for the future clinical development of CAR-T cell therapy in the field of liver cancer[7].

Less suitable for treatment of diseases associated with minors Studies have shown that the expression of chimeric antigen receptor T cell therapy for lymphatic malignancies in children is not ideal. Children and adolescents with high-risk (metastatic and recurrent) solid tumors have a poor prognosis despite intensive multimodal therapy and urgently need new treatment strategies. Adoptive cell therapy (ACT) has shown activity in a variety of adult cancers and there is an opportunity to expand the use of this therapy in children. The use of immunotherapy in pediatric populations has achieved only limited overall clinical trial results, and the success to date has been largely limited to antibody-based therapies and chimeric antigen receptor T-cell therapies for lymphatic malignancies. As research learn about the well-engineered cellular and molecular mechanisms involved in ACT, this will provide biological insights and improved ACT strategies for pediatric malignancies. This review highlights ACT strategies other than chimeric antigen receptor T cell therapy, including completed and ongoing clinical trials, and highlights promising preclinical data in tumor-infiltrating lymphocytes that enhance the clinical efficacy of ACT for high-risk childhood solid tumors [8].

The rate at which older people can receive this treatment is not high. In an article on the practical applicability of chimeric antigen receptor T-cell therapy in older adults with relapsed and/or refractory multiple myeloma, I found the suitability of the therapy for older adults. In 2021, the US FDA approved idecabtagene viontose, the first chimeric antigen receptor-T cell (CAR-T) therapy for patients with relapsed/refractory multiple myeloma (MM) who have previously received at least four lines of therapy. Approval of the Phase II KARMMA trial based on this drug showed a response rate of 73% and a median progression-free survival of 8.8 months; In this case, the power parameters are considered transformative. Other CAR T cell therapies are being tested in similar populations. However, it is unclear what percentage of real-world MM patients, especially older adults, are eligible for this treatment. The trial concluded that less than 10 percent of newly diagnosed older adults with MM are expected to be eligible for CAR-T therapy based on current FDA approval and eligibility criteria. At the same time, a much higher percentage of patients died before reaching CAR-T eligibility. These findings underscore the need to explore CAR-T cell therapies in populations with early-stage disease and better representation of real-world patients to expand the applicability of this new therapy[9].

4. Factors that affect treatment

4.1. Analyse of diseases factors.

It can be seen that chimeric antigen receptor T cell therapy is suitable for related hematologic tumors, systemic B-cell lymphomas with secondary central nervous system involvement, primary liver cancer, partially restricted solid tumors, etc., and it is not very suitable for the treatment of adolescents and the elderly. It is not suitable for some solid tumors, the main reason why it is unstable and easy to off-target, that may mistakenly select correctly expressed cells, and there are certain risks and uncertainties. The main mechanism of action of CAR-T is that T cells and tumor antigens bind to antigens and antibodies through the recognition of antigens and antibodies, and kill tumor cells through T cells. However, there are fewer tumor-specific antigens found so far, most of which work through tumor-associated antigens, and tumor-associated antigens can also be expressed on normal

tissue cells and even important tissues and organs]. CAR-T modified T cells not only have high affinity for tumor target antigens but also have different degrees of affinity for normal tissue cells, resulting in abnormal immune responses to them by recognizing and binding antigens of these normal tissues in the process after CAR-T treatment, causing different degrees of damage to tissues and organs, that is, causing the so-called "off-target effect". At present, CD19CAR-T, the most studied and mature, not only kills malignant tumor B cells but also kills normal tissue B cells, resulting in abnormal development of body B cells, resulting in body disorders. Fortunately, however, abnormal B cell development can be controlled by substitution therapy with immunoglobulin infusion[10].

4.2. Analyse of age factors.

Regarding its inefficient and uncertain treatment of children and the elderly, I can speculate that due to incomplete development or partial failure of body organs, resulting in more obvious cytokine release syndrome (CRS) Almost all patients will have different degrees of CRS, mainly manifested as nausea, headache, palpitations, high fever, hypotension, hypoxia, tissue and organ hypoxia, severe dyspnea, renal failure, coagulation dysfunction, mainly due to the activation and proliferation of a large number of T cells infused into the body, T cells, B cells, NK cells, monocytes/macrophages and other cells mediate the production of a large number of cytokines and chemokines, such as interleukin 6 (IL-6), tumor necrosis factor α (TNF- α), interferon γ (IFN- γ), IL-1b, IL-2, IL-8 and IL-10 lead to systemic inflammatory response. This is unbearable for children and the elderly [11,12].

5. Conclusion

In general, this article aims to study the suitable population of chimeric antigen receptor T cells, and summarize them by reading the literature. From the perspective of the whole text, the cancer treatment method is mainly suitable for the treatment of hematological tumors and some solid tumors, but because the degree of organ development is not suitable for the treatment of most cancer diseases in the elderly, adolescents and children, but the treatment adaptability for myeloma in the elderly is very high. In general, this article talks about the suitability of some cancers to the treatment method through a limited space, and makes a certain analysis of the use of this method, which is probably helpful for treatment. The disadvantage is that the limited text cannot list various cancer pathologies for analysis, and many of the pathologies listed are only based on the clinical report of the paper, not my own field research and data collection, but only a part of the clinical research summary plus their own inference, there are not many papers on the website for reference, and there are not even papers in this regard. It is hoped that in the future, someone will have the ability to analyze the relevant acceptance qualifications and inadaptability of the therapy one by one to achieve more complete and comprehensive results. And later, can also conduct more in-depth research on this aspect, for example, specifically exploring the cause of a certain unadaptive non-expression trait, which is closely related to pathology. And hope that in the future more people can pay attention to the field related to cancer treatment qualifications, because according to the number of papers, this field has not received widespread attention, relatively speaking, which may also be related to the fact that most cancers are inherently incurable..

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